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Review Article

World Journal of Molecular Medicine

Microglia Mechanobiology under the Impact of Intrinsic and Extrinsic Forces During Neurodegenerative Diseases and Traumatic Brain Injuries

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Submitted: 09 July 2024 **Accepted:** 16 July 2024 **Published:** 22 July 2024

Citation: *Svetlana Volodarets (2024) Microglia Mechanobiology under the Impact of Intrinsic and Extrinsic Forces During Neurodegenerative Diseases and Traumatic Brain Injuries. Wor Jour of Molecu Medicine 1(3), 01-14.*

Abstract

Microglia are known for providing immune responses as residential macrophages of the Central Nervous System. However, they tend to become pro-inflammatory in the brain under the mechanical forces expressed by brain tissues during neurodegenerative diseases. These mechanical forces can be divided into intrinsic and extrinsic categories depending on whether they impact the organism from within or outside. Both types of forces transform the mechanical properties of the substrate. Intrinsic forces have a long-lasting impact on microglia, lasting for months or even years, as seen in Alzheimer's or Parkinson's diseases. These forces are connected directly to the mechanical characteristics of the substrate, such as the stiffness of Aβ proteins or α-synuclein proteins.

On the other hand, extrinsic forces are short-term, lasting only a few minutes, and come from outside the organism, such as in traumatic brain injuries. These forces induce shear stress and strain and change the substrate's stiffness. This review delves into the difference between the microglia mRNA gene profile under intrinsic vs. extrinsic forces. The mechanism of direct and non-direct impact of the substrate stiffness on microglia morphology and inflammatory gene profile in Alzheimer's and Parkinson's diseases, during microelectrodes implantation, and in the case of traumatic brain injuries are analyzed.

Introduction

Mechanical forces *in vivo* or *in vitro* environments regulate macrophages' mechanobiology and functions. Microglia are residential central nervous system (CNS) macrophages that maintain brain homeostasis and provide phagocytosis during inflammation [1-3]. Microglia form a heterogeneous cell population depending on their location and current function. The population types include homeostatic, ameboid, hyper-ramified, and hypertrophic [4-6].

Additional phenotypes that occur during Alzheimer's (AD) and Parkinson's disease (PD) include disease-associated (DAM) and dystrophic microglia [7-9]. During AD and PD, pathological proteins such as tau, *Aβ*, and *α*-synuclein appear due to neuroinflammation. These proteins are significantly stiffer in couples of orders of magnitude than surrounding brain tissues, which first leads to the production by microglia of more and more pro-inflammatory cytokines to phagocytose these proteins.

Then, an excess of pro-inflammatory cytokines causes neurotoxic action, damages the neuron that initiates further neuroinflammation, and again polarizes microglia into a pro-inflammatory gene profile. The microglia's pro-inflammatory reaction to the excessive elastic modulus of pathological proteins highlights the role of mechanical forces in the macrophage's immunological response.

Despite the well-known microglia mechanobiology, understanding the mechanism for the impact of the extrinsic and intrinsic forces remains to be determined. On the one hand, scientists consider intrinsic forces to be the forces in the cell and extrinsic forces to be the forces like the extracellular forces, such as the stretching of the membranes of nearest cells or extracellular matrix (ECM) [10-13].

On the other hand, intrinsic forces can be inside the organism, and extrinsic forces can be outside. These different views do not explain the mechanism of the impact of intrinsic and extrinsic forces on the immunological response of the microglia at the material-substrate level. This review considers two types of mechanical forces related to the engineering properties of the material affecting microglia *in vivo* and *in vitro*. Intrinsic forces are passive forces directly linked to the mechanical properties of the substrate where microglia live, such as the stiffness of the ECM

or the stiffness of the materials used as the substrates for *in vitro* models. These forces impact the microglia in the long term.

Extrinsic forces are active, short-impacted forces. They affect the microglia when the material is actively changed, like during tensile or compression *in vivo* during traumatic brain injury (TBI) or *in vitro* during mechanical tests. Extrinsic forces are indirectly linked to the mechanical properties of the substrate. For example, in TBI, during the hit on the head, the stiffness of the brain tissues decreases. As a result, microglia react with extrinsic forces opposite to intrinsic forces. In the absence of local brain stiffening during TBI, microglia express an anti-inflammatory profile, conversely to the pro-inflammatory profile under intrinsic forces in the case of Alzheimer's or Parkinson's diseases.

This review highlights the difference between intrinsic and extrinsic forces' action mechanisms that modify microglia gene profiles and mechanobiology. Firstly, the difference between intrinsic and extrinsic forces on the microglia differentiation and comparison with monocyte reaction are shown. Second, the microglia gene profile *in vivo* and *in vitro* under the intrinsic forces on substrates with different stiffnesses is analyzed. Finally, the microglia polarization in the case of TBI as an example of both extrinsic and intrinsic forces is described.

Intrinsic Forces vs Extrinsic Forces

Microglia maintain brain homeostasis in a healthy state and provide an immune response during neurodegenerative processes [14-17]. Microglia controls the homeostasis of the brain in both the perinatal period and the adult state. During the perinatal period, microglia regulate the formation of neuronal precursor cells (NPC) by releasing factors such as insulin-like growth factor (IGF-1) and pruning debris of the neurons [18].

Furthermore, in the adult state, microglia equilibria neurogenesis is achieved through synaptic engulfment of the neurons and synaptic pruning [19-21]. In addition, they stimulate a pro-inflammatory astrocyte phenotype via the expression of neurotoxic IL-1α, TNF-α, and C1q factors that promote neuronal and oligodendrocyte death [18, 21, 22].

During inflammation in injuries, microglia protect the brain via phagocytosis of foreign structures in the brain and other immune mechanisms. First, microglia sense the source of infection, e.g., amyloid fibrils as *Aβ* fibrils, α-synuclein, and other distinctive structures [23-25].via mechanoreceptors such as integrins and chemoreceptors such as Toll-like receptors [26, 27]. Then, they move to the source of inflammation and eliminate it via phagocytosis. Finally, integrin's activation via a chain of adhesion proteins leads to actin polymerization and results in microglia's movement. Likewise, the contact between activated integrin and ECM leads to mechanical tensions, called traction forces.

Microglia acquire a phagocytic function for cleaning debris and injured neuronal cells via the expression of pro-inflammatory (M1) and anti-inflammatory phenotypes (M2). Unlike the classification of M1 and M2, microglia change their phenotypes between M1 and M2. Show gene expression heterogeneity while providing a phagocytic function. This mechanism might be interrupted under neurodegenerative processes when microglia become highly mobile and produce cytokines that lead to disease progression [18, 26, 28-35].

Therefore, the modern complex classification of microglia has recently been developed with morphological, epigenetic, metabolomics, and proteomics methods. Recent studies have distinguished homeostatic, ameboid, hyper-ramified, and hypertrophic microglia phenotypes. Microglia morphology is generally triggered by mechanical cues or inflammation changes between ameboid, hyper-ramified, and hypertrophic [35, 37, 38]. The hyper-ramified microglia express an anti-inflammatory gene profile, while hypertrophic in the healthy state and dystrophic under neurodegenerative diseases show pro-inflammatory genes [4, 5, 20, 29, 31, 36, 39].

Microglia heterogeneity allows us to reveal the difference between extrinsic and intrinsic forces during neurodegenerative processes like AD, PD, and TBI. Microglia react by expressing a pro-inflammatory gene profile under intrinsic forces, like increasing the elasticity of β-sheets proteins during neurodegenerative processes. For example, in the healthy aged brain, the shear modulus is about 1-3 kPa, while during pathologies such as AD and PD, the shear modulus of the β-structured *Aβ* fibrils in amyloid plaques and *α*-synuclein in Lewy bodies increases up to 12 GPa (figure 1). This difference between the elastic properties in the brain leads to microglia polarization into hypertrophic and dystrophic with pro-inflammatory profiles [40-42, 45-49]

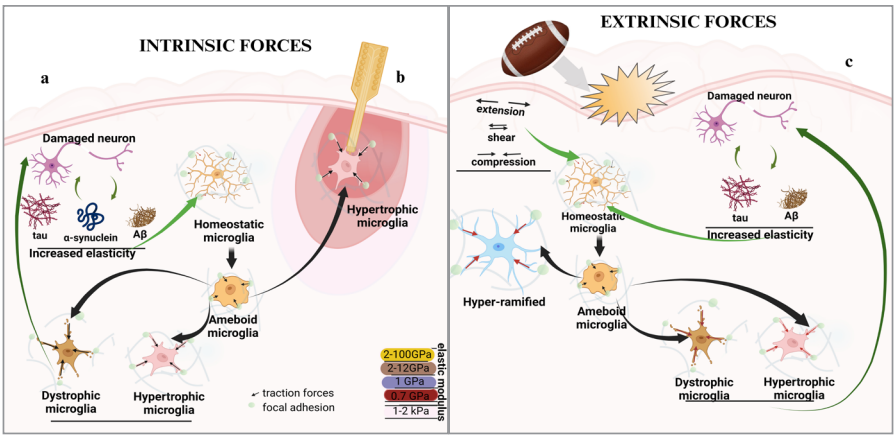

Figure 1: The differences between microglia reactions to intrinsic and extrinsic forces during Alzheimer's and Parkinson's diseases (a), microelectrode implantation (b), and traumatic brain injuries (c) under different stiffness

The foreign bodies (FB) implanted in the brain are another case of unfamiliar structures for microglia in the brain. FBs also have an incredibly high Young's modulus of up to 100GPa, as they are made of metals [50]. Even in the case of carbon FB, Young's modulus is about 10GPa [51]. As a result, microglia also polarize to the hypertrophic phenotype (figure 1). In the next part, we will discuss the reaction of microglia to higher stiffness under neurodegenerative disorders such as AD and PD and during microelectrode implantation.

Under extrinsic outside forces, microglia react by expressing an anti-inflammatory gene profile. *In vivo*, extrinsic forces are created by a mechanical insult like a hit to the head, causing TBIs. Applying forces on the substrate causes stress to be divided into extension, compression, shear, torsion, and bending. During TBI, all five types of stress impact the brain. However, only compression, tension, and shear significantly impact microglia. Compression and tension regulate the stiffness of the material. In the TBI, brain tissues' elasticity decreases, and stress relaxation time increases [52-56].

Microglia react to the decreasing elasticity by providing an anti-inflammatory immunological response in contrast to pro-inflammatory gene expression under the intrinsic forces (figure 1) that can be explained by microglia molecular mechanism to sense the changes in the mechanical environment. Microglia, similar to other macrophages, can feel the high stiffness of the material by Ca^{2+} ion channels mechanoreceptors and transmit the mechanical signal into biochemical response via actin polymerization or to the nucleus via unique biochemical pathways like Yes-associated protein (Yap) signaling pathway that leads to the changing in gene transcription [57-59].

At the same time, the nucleus can sense the mechanical cues in the environment that lead to the nucleus's deformation. Under extrinsic forces that actively impact the substrate nucleus, deformation can even cause DNA damage, especially during the active proliferation of the cells. Nevertheless, evolutionary macrophages have adjusted to the extrinsic forces by decreasing the nucleus deformation by controlling nucleus stiffness [60-64].

The difference between the reaction of microglia on the extrinsic and intrinsic forces needs to be clarified, as proven by the processes that happen during TBI. Immediately after the hit, under tensile, shear, and compression stresses, without local stiffening of the brain (figure 1). Conversely, microglia switch their profile to pro-inflammatory after damaging neurons and releasing tau and *Aβ* fibrils. This leads to an endless loop of neuron destruction, microglia pro-inflammatory polarization, and chronic traumatic encephalopathy (CTE) that have similar clinical pictures to Alzheimer's disease [65, 66].

The answer to the encountered problem can be found in the primary function of microglia. In line with providing phagocytosis, microglia, like other macrophages, move to foreign structures. Since the brain-blood barrier protects the brain from microorganisms, microglia sense more the mechanical cues of the environment than the chemical ones. Scientists report the first activation of Piezo1 mechanosensitive channels before activating TLR family chemically sensitive receptors [67, 68].

This highlights the role of mechanosensing in microglia's attempt to envelop and phagocytose the tau, *Aβ*, and *α*-synuclein. However, microglia fail because the elastic moduli of these proteins go in magnitudes beyond the elastic moduli of surrounding brain tissues. Then, microglia express more and more pro-inflammatory genes that lead to cytokine production, which causes damage to neurons and, in the end, leads to the endless loop of microglia's neurotoxic impact on neurons. Without pathological proteins, microglia express anti-inflammatory gene expression to maintain homeostasis and heal the damaged neurons [69, 70].

It should be noted that microglia express the same anti-inflammatory and pro-inflammatory proteins as monocytes, which are blood vessels' macrophages. Moreover, monocytes demonstrate the same tendency to provide the phagocytic function under extrinsic forces. The example of monocytes can prove the difference between the reaction of macrophages on the extrinsic and intrinsic forces. Even though microglia and monocytes show a similar tendency to extrinsic forces, they react oppositely on the stiff and soft substrates. Monocytes on the substrates with higher elastic modulus express anti-inflammatory proteins such as CD206 but on those with lower elastic modulus, pro-inflammatory proteins such as CD86 [71-73].

Although the microglia express an anti-inflammatory profile on the soft substrates and a pro-inflammatory on the stiff substrates that contradicts the monocyte's polarization on stiff and soft substrates, microglia and monocytes develop similar strategies to overcome the impact of extrinsic forces during evolution. As a result, under the extrinsic forces, microglia express an anti-inflammatory profile, and monocytes release pro-inflammatory gene expression. For example, during TBI, with the decrease in brain elasticity, microglia express the same gene profile as on the soft substrates. Likewise, monocytes demonstrate an identical strategy during the stretching of the blood vessels. They express pro-inflammatory gene profiles, like CD11, because, with the highest tensile stress, the elasticity of blood vessels decreases. In the vitro experiment, monocytes express the same pro-inflammatory mRNA as on the soft substances such as IL-1β and TNF-*α* [74-76].

Hence, the macrophages show a strategy for managing the impact of extrinsic forces based on their reaction to intrinsic forces, such as substrate stiffness. The difference between microglia and monocyte's reaction to intrinsic forces comes from their embryogenesis and location in the adult state. The microglia precursors, primitive macrophages, in the first wave of embryogenesis migrate on the embryonic day 7 (E7.0) to the brain with an elastic modulus of about 1-3 kPa [40, 77-79].

However, precursors of the hematopoietic stem cells from which monocyte-derived macrophages originated in the third way of embryogenesis on the E10.5 migrate to the bones, where the stiffness is about 30 kPa. As a result, each of the macrophages remembers their environment as long-living cells and reacts in a healing, natural manner, anti-inflammatory, in the conditions relevant to the place of their origin [77, 80-83].

Microglia Subpopulations on Substrates with Different Stiffness

Brain mechanical properties vary between healthy and pathological status. The elastic modulus of the brain tissue plays a crucial

role in neurodegenerative processes, especially in aging patients. Hall et al., Budday et al., and Marinval et al. present extended information about brain viscoelasticity. They show that the brain is a non-linear viscoelastic material. The brain tissues respond with reversible deformations on the low mechanical impact and with a plastic deformation replay to the high deformations. Furthermore, various studies investigate and describe the decrease in elasticity in aging brain tissues [38, 40, 79, 84-91].

Nevertheless, in recent publications, there is a gap in the comparison between *in vivo* values of human brain shear modulus in the healthy aging brain, AD, and PD cases from the point of view of microglia reaction to the brain elasticity. We compare the shear moduli (μ) obtained from magneto resonance elastography (MRE) of healthy aged brains and patients with AD and PD. MRE is a widely used technique for diagnosing neurodegenerative processes *in vivo* that uses imaging analysis to extract displacements from the pictures and calculate local stiffness [88, 92-99]. For example, Green M. et al. [100] show that the grey matter on 0.4 kPa is softer than white matter in the healthy aged brain (figure 2 (a)).

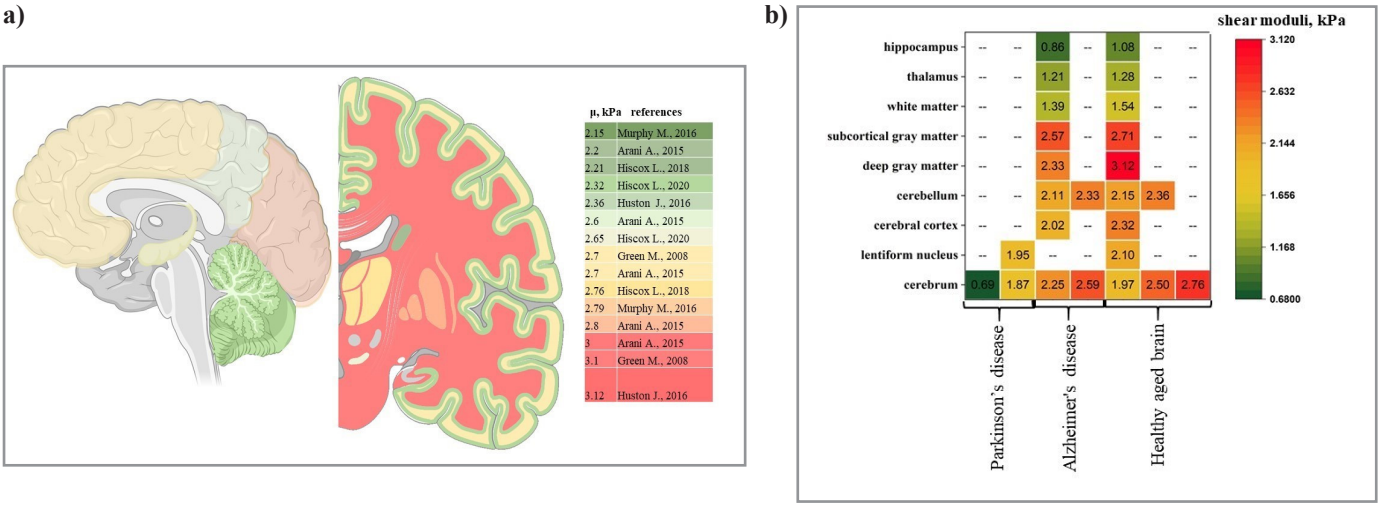

Figure 2: Viscoelastic properties of the brain in health (a) and diseased aged brain (b) with Magnetic Resonance Elastography (MRE) Hiscox, Gerischer, Sack, Murphy, Lipp, μ, shear moduli.

Arani A. et al. [88] and Huston J. et al. [93] reveal that the shear modulus is about 3kPa for deep grey and white matter. As heterogeneous cell populations, microglia change their morphology and gene expression in response to the brain's elastic properties. However, according to Wageningen et al. [101], mice microglia demonstrate the same F-actin expression and morphology in grey and white matter that can be explained by the same shear moduli in grey and white matter. In contrast, in the hippocampus, where the shear modulus is about 2.65kPa, almost like in the thalamus microglia provide their physiological functions of regulation neuroplasticity and phagocytosis. Arani et al. show equal shear moduli for the frontal, pariental and occipital lobs. Even so, the principal place of AD pathology is the frontal lobes, where the tau and *Aβ* plaques appear. They may occur in the parietal lobe and cause microglia activation to the dystrophic and pro-inflammatory phenotypes [40, 92, 95, 102-105].

In the cerebellum, the shear moduli are about 2.2kPa, which is lower than in the hippocampus and allows microglia to provide a neuroplastic function, proving the elasticity's impact on the microglia activation. Similar to the decreasing of the shear moduli in the aging brain during AD and PD, the stiffness of the brain tissues also decreases. In the AD case, Gerischer et al. demonstrate the decreasing of shear moduli in the hippocampus and white matter, while there is no difference in the thalamus (figure 2, b). Likewise, Sack et al. [107] reveal stiffness decreasing in the deep gray matter area. In the case of PD, Lipp et al. [108] found decreasing shear moduli in the lentiform nucleus, the central place of *α*-synuclein pathology, as a slight decrease in the whole brain. Overall, during Alzheimer's disease in the grey matter and cerebellum, the stiffness of the brain tissues decreases, which could be due to the loss of cells during aging. Unlike under Parkinson's disease, the brain's elasticity decreases more than in AD [92, 93, 106, 109].

Despite the decreasing elasticity in the brain during AD and PD, microglia migrate to the destination of higher elastic moduli, such as *Aβ* fibrils and *α*-synuclein. In AD, extracellular β-sheet proteins named *Aβ* fibrils characterized by elastic moduli higher than surrounding appear in the brain that results in a microglia migration due to dividing and engulfing the *Aβ* fibrils in an attempt to phagocytose them (figure 1). Mattana et al. report that microglia find *Aβ* plaques and move to them in the prefrontal cortex due to mechanosensing [8, 23, 42, 110-115].

Indeed, Young's modulus of *Aβ* fibrils variates within the range from 2 to 12 GPa in the studies using indirect techniques such as Brillouin microscopy, high-pressure X-ray diffraction, and statistical analysis of electron images of individual fibrils of *Aβ* plaques. In contrast, Poma et al. [118] calculated shear stress as 1.6 GPa for *Aβ*42 and 0.7 GPa for *Aβ*40. PD is one more aging disease. In PD, *α*-synuclein is a prion protein that accumulates in the brain in the form of Lewy bodies during aging. *α*-synuclein changes elastic moduli, unlike the other brain, similar to

Aβ fibrils. *α*-synuclein has transformed the *α*-helix structure into β-sheet fibrils that formed greater clusters during disease progression [42-44, 116-119].

Studies reveal the range of human *α*-synuclein Young's moduli from 0.6 GPa, 1.3-2.1 GPa to 3 GPa determined by AFM. In addition, Lamour et al. report Young's moduli of mice prion fibrils with a limit of 0.71 GPa determined by AFM. Finally, the brain's elasticity in the white and grey matter is about 2.5 kPa (figure 2 (a)), which is of less magnitude than abnormal structures in AD and PD. Thus, the extent of elastic and shear moduli by *Aβ* fibrils and *α*-synuclein compared to the rest of the brain may explain microglia differentiation to the pro-inflammatory phenotype under PD and AD with the production of neurotoxic cytokines [45, 118, 120].

Microglia homeostatic mRNA factors are downregulated, while pro-inflammatory factors are upregulated in AD and PD *in vitro* and *in vivo* experiments. For example, Kenkhuis et al. demonstrate decreasing gene expression of homeostatic factors such as purinergic G-protein-coupled receptors (P2RY12, P2X4R) and TMEM119 in microglia near *Aβ* plaques. Likewise, Bennet et al. report a decrease of TMEM119 in the mice LPS-activated microglia, which aligns with Vankriekelsvenne et al. and Wageningen et al. Alternatively, the pro-inflammatory factors are upregulated in reactive microglia *in vivo*. Bolós et al. report the upregulation of G-protein coupled receptor CX3CR1 mRNA in reactive microglia in the response of *Aβ*. In addition, ionized calcium-binding adapter molecule 1 (Iba1) is upregulated in the reactive microglia in AD patients. In the same way, IBA1 is regulated in the PD mice models [122-127]. This corresponds with the physiological microglial behavior during AD and PD described in the previous subsection.

In vitro, microglia polarization on the soft and stiffer substrates varies among studies. Whereas Bollman et al [128]. discovered that on the soft polyacrylamide (PAA) gels (0.3 kPa), microglia present round or ameboid shape with fewer processes, while on the stiffer substrates such as 1 and 10 kPa, microglia have long processes and lamellipodia. In contrast, Moshayiedy et al. found that on the substrates with 10 kPa, microglia have round morphology with short processes and lamellipodia [129]. The mRNA analysis confirmed the pro-inflammatory phenotype on the PAA substrates with elastic moduli 10 and 30 kPa. Markers of microglia reactivity, such as CD97 and PPARγ, receptors mediating microglia reactivity, such as TLR4 and TREM1, and receptors involved in microglia adhesion and migration CD9 and CD97 were upregulated on the stiffer substrates (figure 3).

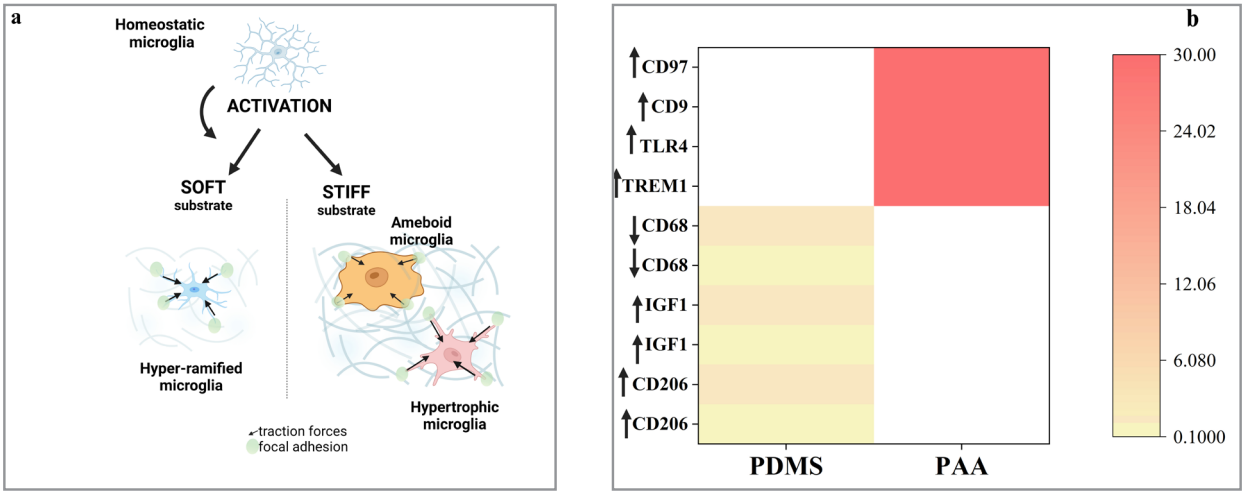

Figure 3: Microglia morphology and mRNA expression on the substrates with different Young's moduli, kPa

Blaschke et al. [130] show that on 0.6 kPa and 1 kPa PDMS substrates, microglia in the cultures with astrocytes have elongated form, and on glass with 1.2 MPa, microglia showed ameboid morphology. Simultaneously, microglia express CD206 and downregulated CD68 on the soft substrates (PDMS, 0.6 kPa), which proves microglia polarization to the M2 phenotype. In another work, microglia cocultured with neurons and astrocytes on the collagen-like protein-polyethylenglykol (CLP-PEG) (144.5 kPa) gels demonstrated small bodies, more processes and longer lamellipodia. In contrast, on collagen substrates (151.1 kPa), microglia have ameboid morphology due to insufficient growth of neurons [131].

In addition, Dudiki et al. demonstrate the same result of microglia morphology and phenotype on the retina used as *in vitro* substrate. Microglia has more processes on the substrates with an elasticity of 2 kPa than on the stiffer layer of 6 kPa. Gene profile reveals an increase of CX3CR1 in the inner level of the retina with 6 kPa compared to the upper nuclear level with 2 kPa, as well as downregulation of TGFβ1 and CD68 on the stiff substrates in the CX3CR1-cre; K3f/f/TGFβ1f/f mice line with knockout of kindlin3 and TGFβ1. Apparently, in the wild state, microglia have the reverse picture [132]. Both *in vivo* and *in vitro* studies indicate that the mechanism of microglia reaction to the different stiffness is complex and determined by microglia mechanosensing and mechanotransduction.

Microglia sense the mechanical forces with mechanoreceptors in a healthy state and during neurodegenerative diseases such as AD and PD. Microglia express mechanoreceptors as ion channels like Ca^{2+} selective channels and adhesive molecules like integrins. Notably, Ca^{2+} ion channels such as Piezo family

channels and integrins are activated by *Aβ* fibrils, *α*-synuclein, or tau-proteins that are stiffer than brain tissues. For example, the Piezo1 channel, a well-known mechanoreceptor in AD, first activates in the presence of *Aβ* plaques by sensing changes in the stress of the membrane near the channel [133-137].

Then, the Piezo1 channel, via its interaction with cadherin and catenin, triggers the polymerization of actin into filaments that allow microglia to form lamellipodia. Finally, the cells move to *Aβ* fibrils and phagocytose them. At the same time, Piezo1 activates toll-like immune receptor TLR4, which produces cytokines that injure the neurons [138]. Then, neurons express pathological proteins like *Aβ* that activate microglia. The devious loop continues since microglia are activated by *Aβ* fibrils and produce cytokines that injure neurons and provoke the appearance of new pathological fibrils.

However, the role of the Piezo1 channel in the inflammation in neurodegenerative processes remains unclear. Another study demonstrates the anti-inflammatory role of the Piezo1 channel by the downregulation of TNF-*α* and IL-6 in the LPS-activated microglia [139]. Likewise, Jantti et al. [24] report the increased expression of Piezo1 channels and Iba1, a calcium-binding adapter molecule, responsible for motility and phagocytosis upregulation in the mice treated with Yoda1. This synthetically synthesized molecule activates Piezo1 channels. Similarly, Hu et al. [23] demonstrate that Piezo1 deficiency diminishes microglial phagocytosis of *Aβ in vivo*. These results prove the role of Piezo1 in the phagocytosis of microglia and clearance of *Aβ* fibrils.

Just like Piezo1, channel integrins sense the stiffness of the substrate via a chain of FA complex proteins and then transduce it on actin, which leads to actin polymerization and lamellipodia formation for microglia movement and phagocytosis. Kim C. et al. [68] found that β1 integrin is responsible for changes in microglia migration and morphology during pro-inflammatory response under *α*-synuclein more than TLR2 (Toll-Like Receptor 2) that produces a higher level of cytokines in the diseased affected regions in PD.

In contrast, recent studies underline the role of intracellular adaptors in microglia mechanosensing. In the health state of mice models, Dudiki et al [140]. found that microglial polarization *in vivo* and the responses to stiff substrates *in vitro* require intracellular adaptor Kindlin3 but not microglial integrins. However, in chronic inflammation, kindlin3-integrin, β1 function is pensable for *in vivo* microglial formation of protrusions. Although the microglia motility is still under investigation, on the whole, it is ground on the non-muscle myosin II (NMII) in the actomyosin complex [141-143].

Melo et al. [144] have highlighted that NMIIB knockout microglia show increased Reactive Oxygen Species (ROS) and elevated levels of IL-1β, IL-6, and TNF*α* pro-inflammatory factors (cytokines). In the same study, Myh9 genes coded myosin 9, Myh10 genes responsible for myosin10, and subunits of NMIIA and NMIIB show a strong dependence on the stress generated by the local actin filaments. The authors explain the role of NMIIA in the production of cortical tension as the mechanism for the appearance of new protrusions by microglia.

The integrin-based adhesions during microglia movement lead to the traction forces expressed on the surface. Scientists widely use traction force microscopy (TFM) to study adherent cell mechanobiology, which allows them to measure the traction forces that cells apply in the environment during their adhesion and migration. Although, for the present time, only several studies focused on the microglia traction forces, the role of traction forces in the cell's migration is well-known [128, 145-151].

The microglia produce higher traction forces on the stiffer substrates , which aligns with the other works. Indeed, higher elastic moduli might lead to the activation of integrins, formation of focal adhesions, and, consequently, higher traction forces. Alternatively, when integrins are activated, for instance, by LPS, microglia produce lower traction forces, with the same tendency to increase traction forces on the stiffer substrates [128, 149]. Therefore, further investigation of the microglia traction forces can lead to understanding the microglia polarization and motility on the stiffer substrates like *Aβ* fibrils or *α*-synuclein for use with therapeutic aim.

One of the present methods of maintaining neurological disorders, such as the implantation of microelectrodes in the brain, connects with microglia mechanosensing. Microglia reacts with pro-inflammatory and anti-inflammatory gene expression on the microelectrode's stiffness. Microelectrodes are used to record the electrophysiological activity of the brain. They reveal a potential for treating neurological disorders such as trauma, epilepsy, and Parkinson's disease [152, 153]. However, the over-limit stiffness of the microelectrodes compared to surrounding brain tissues presents the main problem when using them for implantation.

Indeed, microelectrodes are made from metals like aluminum coated with silicon, gold, or platinum, showing Young's moduli of more than 100GPa (figure 1). The carbon fiber or nanotube electrodes decrease elastic moduli to 10GPa. Even so, this elasticity overcomes the brain tissues' elasticity (1-2 kPa) in magnitudes and leads to the inflammatory, titled foreign body response (FBR). Glial cells such as microglia, astrocytes, and oligodendroglia form glial scars that decrease the effectiveness of the electrode or lead to their brokenness [31, 50, 51, 128, 148-155].

Microglia, via an immune response in an attempt to envelop and phagocytose the microelectrode express pro-inflammatory cytokines IL-1 and TNF-*α* that cause astrocyte neurotoxicity. Notably, near the electrode implant (Perforated Polyimide based MEA Platforms (PPMPs) in the moving mice microglia show a pro-inflammatory profile between 14-28 days. PPMPs consist of aluminum, silicon, polyimide yers, and gold electrodes. Microglia changed the ramified homeostatic morphology to ameboid with short lamellipodia and upregulated Iba-1. Conversely, resting microglia are created during the long-term implantation of MEA platforms or hydrogel-coated microelectrodes [156-158].

In fact, during five months of implantation of nanoelectronic thread (NET) (silicon coated with platinum or gold) in the moving mice, resting microglia were found in the mice's postmortem brains. Similar to the previous study, the coating with PEG-DMA hydrogels of electrodes shows decreasing in pro-inflammatory glial genes. Spencer et al. revealed the elimination of glial fibril-

lary acidic protein (GFAP) after eight weeks of implantation of hydrogel-coated electrodes (Young's modulus E=11.6 kPa) compared to glass electrodes. The previous evidence highlights that the microglia expresses a pro-inflammatory gene profile on the substrates with an elasticity higher than the physiologically available mechanical environment. Microglia upregulate mRNA expression on substrates higher than 2 kPa by expressing such pro-inflammatory markers as TLR4 and TREM1 [159, 160].

Extrinsic Forces Impact on Microglia *in Vivo* and *in Vitro*

Traumatic brain injuries (TBIs) present a complex case of extrinsic forces' impact on the microglia *in vivo*. In this case, several factors affect the never-resting immune cells in the brain. First, The type of injury, such as one-time or repetitive, and the post-trauma time, such as acute or chronic, modulate microglia reactivity. It has been shown that microglia become anti-inflammatory and pro-inflammatory during the first hours after trauma in one-time injury [160-163].

In contrast, in the chronic phase and after repetitive injuries, the microglia change their phenotype to pro-inflammatory. Even so, microglia polarization varies among studies. Madathil et al. [164] report the presence of anti-inflammatory microglia phenotype six hours after single or repetitive trauma in the rat crash simulation. In addition, brain tissues change their mechanical properties in TBI after one-time and repetitive trauma [165,166].

Hoursan H. et al. [167] report the one-time trauma brain shear modulus of 1.8 kPa calculated with a finite element model for a young patient compared to 2.7 kPa registered in a health state. However, *Aβ* fibrils and protein tau, the main cause of AD, and neuron *α*-synuclein, the primary reason for PD, appear in the posttraumatic brain in the acute and chronic phases. *Aβ* plaques have been found after acute TBI in the postmortem brain or the brain of TBI survivors after biopsy around contusions. Furthermore, Mez et al. confirm the presence of *Aβ* plaques and *α*-synuclein by immunostaining the postmortem brain samples of retired American football players with CTE [40, 96, 168-170].

The inflammatory process in the tissues near the injury leads to the microglia's pro-inflammatory gene expression, including changes in neurons and astrocytes. Liu et al. report pro-inflammatory phenotype with expression of TNF*α*, IL-1β, and IL-6115 *in vitro* experiments of coculturing needle-scratched neurons with microglia for 24 hours. Notably, all these factors lead to the heterogeneity of the microglia in TBI. Several sub-phenotypes exist between pro-inflammatory (M1) and anti-inflammatory (M2) phenotypes under TBI [40, 65, 67, 96, 161-171]. Hence, the picture of microglia polarization in TBI is still not clear.

Microglia expresses an anti-inflammatory profile during the first hours or days after trauma. Wang et al. [71]. found that microglia started to express CD206, anti-inflammatory phenotype, 1 to 3 days after TBI and increased from 3 to 5 days after injury (figure 4). The expression profile of CD163, another anti-inflammatory marker, is still not well defined.

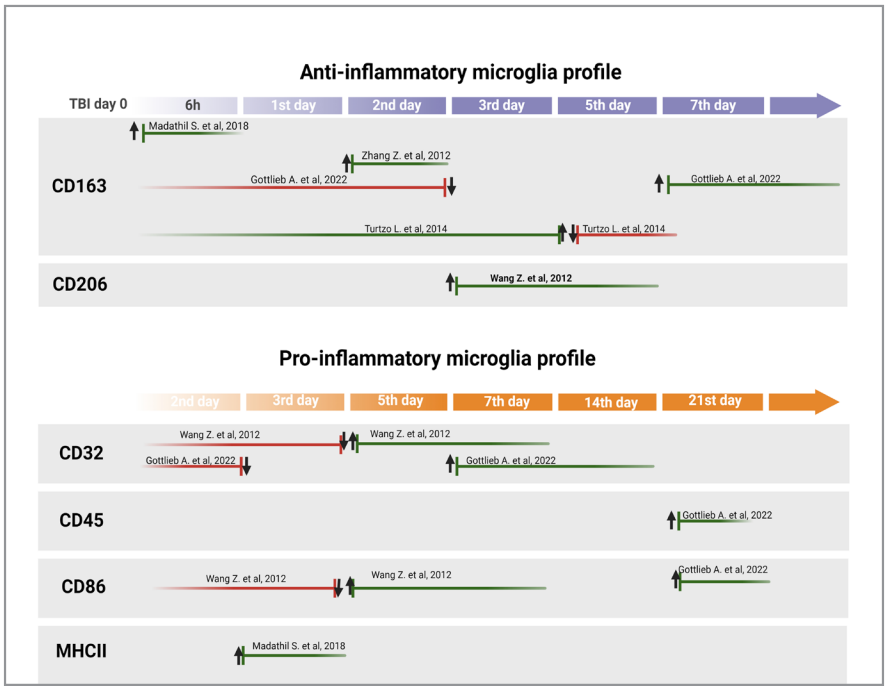

Figure 4: Microglia mRNA expression after TBI

Gottlieb et al. [69] prove that the gradual expression of CD163 decreased until the second day and increased again after the seventh day. In addition, in this study, the homeostatic purinergic G-protein coupled receptor (P2Y12), a homeostatic factor, decreases after 48 hours post-trauma. In contrast, Zhang et al. [172] reported increased expression of CD163 on the second day of TBI, which agrees with results obtained by Turtzo et al. [70] that found an increased expression of CD163, but it further decreased on the fifth day. Interestingly, Madathil et al. [166] revealed increased expression of CD163 by microglia in six hours after single or repetitive trauma in the rat crush simulation with helmet and steel balls.

The data on changes in pro-inflammatory factors is also contradictory. Pro-inflammatory markers decrease in the first days of the TBI and then increase again. Wang et al. [71] reveal that CD32 and CD 86 decreased on the third day and increased again from 5 to 7 days. Along with the previous tendency, in the rat's model, microglia express pro-inflammatory MHC-II genes 72 hours after repetitive concussive injury [166]. In Gottlieb et al.'s research, the CD32 pro-inflammatory marker decreases until the 2nd day, further increasing on the 7th -14th day. However, in the same research, scientists revealed that CD86 and anti-inflammatory CD45 expression in the mice traumatic model increases only on the 21st day after TBI [69].

In addition, in chronic trauma, Grovola et al. found the microglia expression of ramified phenotype with increasing branches in white matter and certain hippocampal areas after 1-year post-injury cases in pigs in chronic stages after mild TBI. Alternatively, in acute trauma, Lier et al. found the different microglia phenotypes from incompletely ruptured pons during an accident that caused immediate death. The postmortem IBA1 immunostaining of microglia shows dystrophy microglia, with short processes and thick soma, and ramified microglia in 50 μm from the damaged tissues [173, 174].

Microglia polarization to an anti-inflammatory profile in the first hours after trauma can be explained by the decrease in elasticity of brain tissues near the traumatic place. It has been shown in animal models that the elastic moduli of the brain tissues in TBI decreases like in the aging processes. For example, E. Kwon et al. [55] demonstrate the decrease in the shear modulus in the postmortem sheep brain 3 hours after acute trauma under uniaxial compression test. Likewise, Shafieian et al. [56] report the decreasing elastic modulus of tissues in the area near the ponto-medullary junction from 7.8 kPa in undamaged rats to 5.9 kPa in rats injured model of traumatic axonal injury during *in vivo* unpreconditioned nanoindentation tests.

Boulet T. et al. [175] demonstrate the decrease of the shear moduli measured by MRE in the rats with TBI, which decreased in the first hours of the trauma. On the other side, from the 7th day, the shear moduli increase up to the first values four weeks after trauma. Indeed, the normalization of shear stress near the injured area in the first hours of trauma aligns with the microglia anti-inflammatory profile described above. Despite decreased brain elasticity due to TBI, pathological proteins such as *Aβ* and tau with extremely high elastic modulus appear and activate the microglia pro-inflammatory gene profile. First, damaged axons in the acute trauma release amyloid precursor protein (APP) that leads to the *Aβ* fibrils accumulation near the damaged axons and further to the formation of the *Aβ* plaques [164, 165, 175-178].

Furthermore, *Aβ* plaques remain present in the white matter of the postmortem human brain not only one year but even 18 years after injury. In this long-standing observation of the single TBI survivors' postmortem brain, Johnson et al. reveal that APP appears simultaneously with CR3/43, one of the pro-inflammatory microglia markers. Second, damaged axons release the tau proteins that also lead to the progress of inflammation and neuronal death. Tau proteins and *Aβ* fibrils, well-known AD markers, are released during encephalopathies after TBI. Finally, microglia polarize to hypertrophic or dystrophic with the expression of pro-inflammatory genes to phagocyte tau proteins [179-181].

Hence, when substrate elasticity decreases due to external forces like hit, microglia express an anti-inflammatory profile. However, during chronic processes in TBI involving the accumulation of pathological proteins with high elasticity, microglia switch to a pro-inflammatory state as part of their normal physiological function.

Conclusions and Open Questions for the Field

Results from multiple studies support the understanding of the difference between the impact of extrinsic and intrinsic forces on the microglia gene expression profile and mechanobiology. While the advances in the findings in the microglia differentiation reveal a pro-inflammatory profile under the intrinsic forces and an anti-inflammatory profile under extrinsic forces, the questions about the mechanism of microglia mechanosensing and mechanotransduction under mechanical forces are opened.

This includes further investigations into the role of Piezo1 in recognizing the mechanical forces and transducing them to the nucleus under intrinsic forces. Next, research in the microglia traction forces *in vitro* experiments is required to prove the central role of decreasing the material elasticity in the microglia polarization. Furthermore, the role of the material properties under extrinsic forces has to be elucidated in further investigations.

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